Remarks/Arguments

Claims 15-23 are pending in this application.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH

A. ENABLEMENT REJECTIONS

I) The Examiner rejected claims 15-23 because the specification while being enabling for GLP-1 [ie GLP-1 (7-37)], does not provide enablement for GLP-1 compounds. In responding to Applicants' arguments in the previous amendment that the specification discloses GLP-1 compounds and how to use such compounds to make the formulations of the invention, the Examiner states that "Applicant's arguments focus almost exclusively on the level of ordinary skill in the art and ignore the essence of the enablement" and that "tossing out the mere germ of an idea does not constitute enabling disclosure". (pages 2 and 3 of Office Action). The Examiner then concludes that "when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art" (page 3 of Office Action).

Applicants respectfully traverse this rejection and strongly disagree with the Examiner's characterization of their previous arguments for enablement as focusing almost entirely on the level of skill in the art and not on the teachings of the present specification.

The single pending independent claim in the present application is directed to "A composition comprising not less than about 10 mg/ml of a GLP-1 compound and a phenolic or an alcoholic aromatic compound, where said composition is a gel having thixotropic properties".

The present specification teaches that such compositions can be prepared by mixing the GLP-1 compound in a concentration within a certain range with a phenolic or an alcoholic aromatic compound such as those described on page 3, lines 24-26 in an aqueous medium (page 3, lines 20-22 and page 4, lines 8-13) and provides 4 examples of the production of such compositions. The specification further teaches that the compositions produced by following the teachings of the invention can be evaluated for their gelling and thixotropic

properties by the specific tests described on page 5, line 9 to page 6, line 14. Thus, the present application, not the state of the art, discloses the components, and the concentrations of such components, to utilize in making the claimed compositions as well as specific tests that can be utilized to evaluate the gelling and thixotropic properties of such compositions. Applicants therefore submit that the present specification has done far more than "tossing out the mere germ of an idea". Indeed, the case from which the aforementioned quote was taken, Genentech v. Novo Nordisk [42 USPQ2d 1001 (Fed. Cir. 1997)], can be readily distinguished from the teachings provided by the instant specification.

In Genentech, the Federal Circuit held that a claim to a method of producing human growth hormone (hGH) using cleavable fusion expression was nonenabled. The court based its holding inter alia on its findings that the Genentech application provided no reaction conditions for the steps needed to produce hGH nor a description of any specific cleavable conjugate protein and that the single enzyme listed as a possible cleavage agent (trypsin) was indicated by a British patent to be unsuitable for the cleavable fusion expression of Arg-containing proteins such as hGH. Genentech at 1004-1005. In addition, the court noted that no one had been able to produce any human protein via cleavable fusion expression as of the application filing date and that the method was not used to make any human protein for nearly a year after the filing date and hGH for 5 years. Genentech at 1006.

By comparison, as discussed above, the pending claims in the present application are directed to "a composition comprising not less than about 10 mg/ml of a GLP-1 compound and a phenolic or an alcoholic aromatic compound, where said composition is a gel having thixotropic properties" and the present specification teaches specific concentrations of GLP-1 compound that can be used to make the claimed composition as well as specific phenolic or alcoholic aromatic compounds that can be included in such compositions. Further, the present specification provides specific working examples of conditions under which such compositions can be made and specific tests by which their gelling and thixotropic properties can be evaluated. Thus, in contrast to the Genentech application, the present application provided specific details and working examples of the conditions by which the claimed compositions can be made.

In addition, and in further contrast to the Genentech application, the present application discloses the materials which can be used to make the claimed compositions.

As discussed above, the present application provides examples of a phenolic or an alcoholic aromatic compound which can be used to make the compositions of the invention

where such compounds were widely known and available to those skilled in the art (see page 3, lines 24-26 of the specification).

With respect to "GLP-1 compounds", the specification teaches that GLP-1 (7-37) and GLP-1 (7-36) amide and analogues and functional derivatives thereof are designated "GLP-1 compounds" (sentence bridging pages 1-2) and that examples of " GLP-1 compounds" includes polypeptides comprising the 7 - 34 amino acid sequence of GLP-1, viz. formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys

(I)

or a peptide sequence derived from formula I without eliminating the GLP-1 like activity (page 3, lines 10-16) where with respect to "GLP-1 activity", the application teaches that GLP-1 is known to stimulate insulin release (see page 1, lines 19-21). . The term GLP-1 compound is also disclosed to include derivatives of such polypeptides such as acid addition salts, carboxylate salts, lower alkyl esters, amides, lower alkyl amides and lower dialkyl amides. (page 3, lines 16-18).

Thus, the specification teaches that by "GLP-1 compounds" is meant GLP-1 (7-37) and GLP-1 (7-36) amide and analogues and functional derivatives thereof and that examples of such compounds include polypeptides comprising the 7 - 34 amino acid sequence of GLP-1, viz. formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys

(I)

or a peptide sequence derived from formula I, where such peptides are able to stimulate insulin release. Accordingly, the present application discloses the GLP-1 compounds that can be used to formulate the compositions of the invention.

Moreover, this teaching is supplemented by, rather than substituted by, the fact that as of the 1994 Danish priority filing date, analogs and derivatives of GLP-1 (7-37) and GLP-1 (7-36) amide having GLP-1 like activity (ie the ability to stimulate insulin release) were clearly known and publicly available to those skilled in the art as were as methods for preparing such compounds (see, for example, US patents 5,545,618, 5,188,666 and 5,120,712). Thus, in contrast with the Genentech application and with the Examiner's

assertion in the present Office Action, the present application teaches both the materials and the conditions necessary to produce the claimed compositions

Faced with the above teachings, the Examiner's position appears to be that undue experimentation would be required to make compositions containing GLP-1 compounds other than GLP-1 (7-37). [see paragraph bridging pages 3-4 of July 15, 2002 Office Action where the Examiner asserted that since the specification only provides working examples for GLP-1 (7-37), it would involve undue experimentation to determine if the claimed compositions could be produced using other GLP-1 molecules with sequences different from GLP-1 (7-37)].

However, the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

As discussed above, the present specification teaches specific concentrations of GLP-1 compound that can be used to make the claimed composition as well as specific phenolic or alcoholic aromatic compounds that can be included in such compositions and provides specific working examples of conditions under which such compositions can be made and specific tests by which their gelling and thixotropic properties can be evaluated.

Moreover, while the present application provides working examples with only a single GLP-1 compound [GLP-1 (7-37)], the specification clearly teaches other GLP-1 compounds that can be used to produce the compositions of the invention. Accordingly, it is Applicants' position that in view of the teachings of the present specification it would involve only routine experimentation to produce a composition of the invention with a GLP-1 compound other than GLP-1 (7-37).

Thus, Applicants submit that the present application clearly enables one skilled in the art to produce the compositions of the invention with GLP-1 compounds other than GLP-1 (7-37) without undue experimentation and withdrawal of the section 112, first paragraph rejection is therefore respectfully requested.

B. WRITTEN DESCRIPTION REJECTION

The Examiner rejected claims 15-23 on the basis that the term "GLP-1 compound" does not describe the common attributes or characteristics that identify members of the genus" (page 4 of Office Action). With all due respect, Applicants disagree.

In considering whether the written description requirement has been satisfied, the fundamental inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date of the application, the applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc. v. Mahurkar, 19 USPQ 2d 1111, 1117 (Fed. Cir. 1991).

Here, as discussed above in response to the enablement rejection, the specification teaches that by "GLP-1 compounds" is meant GLP-1 (7-37) and GLP-1 (7-36) amide and analogues and functional derivatives thereof and that examples of such compounds include polypeptides comprising the 7 - 34 amino acid sequence of GLP-1, viz. formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys

(I)

or a peptide sequence derived from formula I, where such peptides are able to stimulate insulin release. Thus, the specification clearly provides common structural [the sequence of formula I and the publicly known sequences of GLP-1 (7-37) and GLP-1 (7-36) amide and analogs and derivatives thereof] and functional (the ability to stimulate insulin release) attributes that identify members of the genus "GLP-1 compounds".

Moreover, that those skilled in the art as of the filing date of the present application clearly have understood what is meant by analogs and derivatives of GLP-1 (7-37) and GLP-1 (7-36) amide having GLP-1 like activity is clearly evidenced by US patents 5,545,618, 5,188,666 and 5,120,712 which provide numerous examples of such molecules.

Accordingly, Applicants submit that the phrase "GLP-1 compounds" as used in the specification and claims fully complies with the written description requirement of 35 USC 112, first paragraph and withdrawal of this rejection is therefore respectfully requested.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 112 SECOND PARAGRAPH

The Examiner rejected the claims under section 112 second paragraph as being indefinite in the use of the phrase "GLP-1 compound" because "neither 'analogs and functional derivatives of GLP-1' nor 'GLP-1 compound' identifies that material element or combination of elements which is unique to, and therefore definitive of a GLP-1 compound" (page 4 of Office Action).

Applicants respectfully traverse this rejection.

As set forth in MPEP 2173.02, definiteness of claim language is analyzed in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Here, as discussed above in response to the enablement rejection, the specification teaches that by "GLP-1 compounds" is meant GLP-1 (7-37) and GLP-1 (7-36) amide and analogues and functional derivatives thereof and that examples of such compounds includes polypeptides comprising the 7 - 34 amino acid sequence of GLP-1, viz. formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys

(I)

or a peptide sequence derived from formula I, where such peptides are able to stimulate insulin release.

Moreover, the prior art as of the filing date of the present application clearly demonstrated that those skilled in the art understood what is meant by analogs and derivatives of GLP-1 (7-37) and GLP-1 (7-36) amide having GLP-1 like activity (see, for example, US patents 5, 545,618, 5,188,666 and 5,120,712).

Thus, Applicants submit that in view of the contents of the present application and the teachings in the art, the phrase "GLP-1 compound" as used in the specification and

claims clearly apprises one of ordinary skill in the art of its scope and, therefore, fully complies with the requirements 35 U.S.C. 112, second paragraph.

Accordingly, Applicants respectfully request withdrawal of the section 112 second paragraph rejection.

REJECTION OF THE CLAIMS UNDER 35 U.S.C. 103

The Examiner rejected claims 15-23 under section 103 as being unpatentable over Danley in view of Avis and further in view of Galloway, Schott and Ballard.

Danley is cited as teaching that prolonged delivery formulations of GLP-1 can be formulated with compositions comprising GLP-1 (7-37), a phenolic compound and zinc; Avis as teaching that antimicrobial agents must be added to multi-dose parenteral preparations and that phenol is a suitable antimicrobial agent; Galloway as teaching that only a small quantity of zinc is required to precipitate a significant portion of GLP-1; Schott as teaching that thixotropy can be useful in the formulation of pharmaceutical suspensions and emulsions; and Ballard as giving a clear indication of success in designing a prolonged action preparation with thixotropic pellets.

The Examiner therefore concludes:

"it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a composition comprising GLP-1, a phenolic compound, and zinc, as taught by Danley in view of Avis, and to modify that teaching by making a thixotropic composition, as taught by Schott and/or Ballard, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because only a small quantity of zinc is required to complex with and precipitate a significant portion of GLP-1 and a thixotropic composition would prevent sedimentation and claying of the precipitated GLP-1 particles". (page 7 of Office Action)

Applicants respectfully traverse this rejection.

Applicants do not dispute that thixotropy can be used in the production of pharmaceutical formulations (Schott and Ballard). However, to set forth a prima facie case of obviousness, there must inter alia be some suggestion or motivation in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the

art, to modify the references or to combine reference teachings to produce the **specifically claimed** invention at issue. Moreover, the teaching or suggestion to make the claimed invention must be found in the prior art, and not based in hindsight analysis afforded by applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir.1991).

Here, the single pending independent claim in the present application is directed to "A composition comprising not less than about 10 mg/ml of a GLP-1 compound and a phenolic or an alcoholic aromatic compound, **where said composition is a gel having thixotropic properties**". Thus, in the claimed compositions, the GLP-1 compound and the phenolic or alcoholic aromatic compound must be present in concentrations sufficient to produce a gel with thixotropic properties.

Given that Danley was published October 12, 1994, just two months before the priority filing date of the present application, and that Danley was clearly a person skilled in the art who was interested in the production of prolonged formulations of GLP-1, it is Applicants' position that Danley is the closest cited art to the claimed invention. Thus, it is of interest to the obviousness analysis to note that while Danley disclosed a huge number of ways of preparing prolonged delivery of certain GLP-1 compounds, and was presumably aware of the use of thixotropy from the teachings of Schott and Ballard cited by the Examiner, none of the compositions produced by Danley were gels with thixotropic properties (see page 2, lines 15-20 of the present application).

Stated another way, Danley provides clear and convincing evidence that a person skilled in the art (Danley) **at the time of the filing of the present application** did not think of gels with thixotropic properties as the solution to the problem of prolonged delivery of GLP-1 compounds. Indeed, in this regard, Applicants note that in contrast to the claimed compositions where the concentration of GLP-1 compound must be not less than 10mg/ml, the formulations of Danley which do contain GLP-1 and phenol and/or zinc all contain GLP-1 of less than 10 mg/ml.

Faced with this failure of Danley, one skilled in the art in the specific art area to which the present invention is directed (prolonged delivery of GLP-1 compounds), to

disclose gels with thixotropic properties as the solution to the problem of prolonged delivery of GLP-1 compounds, the Examiner nevertheless asserts that in view of multiple references that disclose individual elements of the claimed compositions (Avis-phenol; Galloway-zinc; and Scott and Ballard; thixotropy), it would have been obvious to modify the teachings of Danley to obtain the claimed compositions.

In reply, it is Applicants' position that the combination of Danley with Avis, Galloway, Schott and Ballard is a clear example of an obviousness rejection based on the improper use of hindsight afforded by the present application to selectively pick and choose elements of the claimed compositions from the prior art. For example, while Ballard discloses thixotropy as one means of producing a prolonged action pharmaceutical, this reference also discloses numerous other methods by which such prolonged action may be obtained.

More importantly, Applicants submit that the present obviousness rejection begs the question of why, if it was so obvious to modify the teachings of Danley in view of Avis, Galloway, Schott and Ballard to produce the claimed compositions, that Danley himself, a person clearly skilled in art of prolonged delivery of GLP-1 compounds at the time of filing of the present application, did not do so and disclose gels with thixotropic properties among his numerous compositions for prolonged delivery of GLP-1 compounds.

Finally, Applicants note that the Examiner's citation of Galloway as teaching that only a small quantity of zinc is required to **precipitate** a significant portion of GLP-1 is **not** consistent with the use of zinc to produce the presently claimed compositions since a critical element of the claimed compositions is that they are gels with thixotropic properties.

Specifically, while a gel is a colloidal system of particles suspended and dispersed throughout a liquid, precipitation occurs when a solid material comes out of a solution or suspension. Thus, the teaching in Galloway of concentrations of zinc that would precipitate GLP-1 out of solution actually teaches away from the use of zinc to produce the claimed compositions (ie a gel with thixotropic properties) and would not motivate one skilled in the art to produce a gel using zinc.

Accordingly, in view of the above remarks, it is submitted that the claimed compositions are nonobvious over the cited art and withdrawal of this obviousness rejection is therefore respectfully requested.

In view of the above remarks, Applicants respectfully submit that this application is in condition for allowance and early and favorable action by the Examiner to that end is solicited.

Respectfully submitted,

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